IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Galit LEVIN et al.	Confirmation No.: 7071
Application No.: 10/580,875	Group Art Unit: 1615
Filing Date: March 15, 2007	Examiner: William A. Craigo
For: TRANSDERMAL SYSTEM FOR SUSTAINED DELIVERY OF POLYPEPTIDES	Attorney Docket No.: 85189-13700

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop : AF
Commissioner for Patents
P.O. Box
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Sir:

Applicant requests a panel review of the decision of the Examiner mailed June 23, 2011, rejecting claims 34-51 and 54-61 of the above-identified application.

The claims were rejected as unpatentable over U.S. Patent No. 6,148,232 to Avrahami (referred to hereafter as "Avrahami"), in view of U.S. Patent No. 6,275,728 to Venkatraman et al. (referred to hereafter as "Venkatraman") in view of U.S. Patent No. 5,983,130 to Phipps et al. (referred to hereafter as "Phipps") in view of U.S. Patent No. 5,418,222 to Song et al. (referred to hereafter as "Song") in view of U.S. Patent No. 5,158,537 to Haak et al. (referred to hereafter as "Haak") in view of U.S. Patent No. 5,906,830 to Farinas et al. (referred to hereafter as "Farinas").

As disclosed in the application and as explained throughout prosecution, the present invention relates to a method for sustained transdermal delivery of a therapeutic or immunogenic peptide, polypeptide or protein by generating a plurality of micro-channels in a region of intact skin of a subject; affixing a patch comprising said therapeutic or immunogenic peptide, polypeptide or protein embedded in a matrix of a hydrophilic polymer to said region of skin; and achieving a therapeutic concentration of the peptide, polypeptide, or protein in the subject's blood for at least 6 hours based on the delivery of said peptide, polypeptide or protein solely by diffusion from the patch through the micro-channels to the blood. None of the references teaches or suggests these novel features of the presently claimed method.

Avrahami discloses a device for generating micro-channels in the stratum corneum of the skin, and that device is then removed from the skin in order to enhance the transdermal delivery

of a substance that is subsequently placed on the skin. The Examiner is correct in stating that "Avrahami expressly teaches 'preferably, micro-channels allow the diffusion therethrough of large molecules at a greater rate than the same molecules would diffuse through pores generated by electroporation," but Avrahami provides neither a size range nor other characteristics for the "large molecule" it refers to, let alone defining the "large molecule" as "peptide, polypeptide or protein," as presently claimed. The only clue Avrahami gives a person of ordinary skill in the art regarding the "large molecule" is that it is a drug that can be supplied by a "commereially avalaible medical patch." (See Avrahami at col. 12, ll. 32-33). It should be emphasized, however, that skin patches for peptides, polypeptides or proteins were not commercially available at the filing date of the present application and such patches are not commercially available even at the present time, so that this is not what Avrahami contemplated by that statement. The transdermal delivery through skin from a patch of peptides, polypeptides or proteins was generally known to skilled artisans to be negligible prior to the present invention. A skilled artisan would expect to achieve even less delivery if the peptide, polypeptide or protein is embedded in a polymeric matrix in the patch. Thus, to the best of Applicant's knowledge, no one has ever made any skin patch comprising a peptide, polypeptide or protein embedded in a polymeric matrix, commercially or otherwise, as it would not be expected to be a useful product. Nor would one consider using such a product in combination with Avrahami's disclosure.

The Examiner errs in stating that "(w)hether Avrahami utilizes a commercially available skin patch is irrelevant to the claim..." (See the Final Office Action, at page 2, last paragraph). As a matter of fact, the type of the skin patch is critical and very relevant to the presently claimed method because the unique combination of generating micro-channels in the skin of a subject and affixing the specific patch which comprises a drug reservoir layer which is a matrix of a hydrophilic polymer and a pharmaceutical composition comprising a peptide, polypeptide or protein, makes it now possible to achieve sustained transdermal delivery of said peptide, polypeptide or protein in a manner that could not previously be achieved.

The Examiner also errs in alleging that paragraphs [0017] and [0059] of the published application do not provide support for a method whereby passage of peptides, polypeptides or proteins occur by diffusion only (See *id.* at page 3, second paragraph). Specifically, paragraph [0017] of the published application clearly discloses that the active agent released "from the polymeric drug reservoir layer" of the patch is delivered "through the micro-channels to the

systemic circulation over extended periods of time." As such, no electrical energy is applied to the patch to iontophoretically deliver the active agent. In addition, claim 34 specifically recites and claims that the delivery of the peptide, polypeptide or protein from the patch into the skin is by diffusion only. Thus, the Examiner's argument that "the claim is not so narrow to be limited to diffusion only," is incorrect and cannot be sustained in light of the present claim language.

Acknowleding that Avrahami does not disclose particular skin patches, the Examiner cites five other patents describing electroporation devices and transdermal delivery devices including sustained release transdermal delivery devices. None of the secondary references cited by the Examiner includes disclosure that remedies the deficiencies of Avrahami.

First of all, Venkatraman, Phipps, and Haak disclose electrotransport drug delivery devices which require application of electrical energy to the drug composition so as to iontophoretically deliver the drug into the subject's body. In particular, Venkatraman discloses a hydratable drug reservoir film for electrotransport drug delivery devices; Phipps discloses an electrotransport agent delivery device for delivering a therapeutic agent through a body surface; and Haak discloses a dry-state iontophoretic drug delivery device having drug and electrolyte reservoirs. In contrast, Avrahami specifically states that the method disclosed therein, "(u)nlike methods of electrically promoted drug delivery known in the art, such as iontophoresis and electroporation, . . .enables relatively large channels to be formed, through which even large molecules of the active substance can pass rapidly, without the necessity of ionizing or polarizing the molecules." (See Avrahami at col. 3, ll. 14-20). Thus, one of ordinary skill in the art, reading Avrahami, would not be motivated to combining the teachings of Avrahami with those of Venkatraman, Phipps, and Haak as they are non-analogous art.

Moreover, Song discloses single and multiple layer collagen films useful for wound dressing, NOT for transdermal delivery on unwounded skin, as presently claimed. The Examiner errs in stating that Song "is not limited to wound, burn or trauma sites." (See the Final Office Action, at page 4, second paragraph). As a matter of fact, Song explicitly states that "(t)he present invention provides a much desired improvement in **wound** dressings by providing for such a steady, even, and continuous release of therapeutic agents over an extended period of time." (See Song at col. 2, ll. 11-16, *emphasis added*). Thus, Song only discloses drug delivery to wound, burn or trauma sites. (See *id.* at col. 2, ll. 50-60 and col. 6, ll. 19-36). Therefore, a skilled artisan would not look to Song for teachings for applying a drug to intact skin in which

micro-channels have been generated, but instead for assistance in treating damaged skin, where there are ample lesions for the diffusion and absorption of the drug as a result of the damaged skin.

Regarding Song, the Examiner alleges that "Song *et al.* also disclose that electroporation, by itself, does not deliver drug, it prepares the tissue for delivery of drug by other means, including iontophoresis (Column 3, lines 37-42)," and that "Song *et al.* further disclose delivery of insulin and HGH for transdermal electrotransport delivery of peptides and polypeptides (Column 13, lines 39-50)." Song does not refer to iontophoresis in col. 3, lines 37-42, however, nor does he disclose delivery of insulin and hGH for transdermal electrotransport delivery of peptides and polypeptides in col. 13, 39-50. As explained hereinabove, Song does not teach any transdermal delivery at all: this is a feature of the present invention and not by Song.

Finally, Farinas discloses a manufacturing method for preparing supersaturated drug reservoirs wherein the drug-polymer admixture comprising polymeric materials such as getalin and carrageenan is heated to a temperature that dissolves the drug in the polymer. The drug in Farinas cannot be a peptide, polypeptide or protein because heating of such agents to the melting temperature of the drug-polymer (e.g., 109°C or even to 140 °C as exemplified in Example 2 of Farinas) would certainly denature the peptide, polypeptide or protein that is embedded in the polymeric matrix of the patch and consequently would destroy its activity. Farinas thus teaches a method that is a totally undesirable end result for the presently claimed invention.

The Examiner incorrectly asserts that "(s)imple peptides encompassed by the claims would not be denatured." (See the Advisory Action dated September 29, 2011, at page 4, second paragraph). In contrast, it is well known in the art that heat causes the denaturation of peptides. For example, the self-assembling peptide RADA16-I, which is a simple peptide with only 16 amino acids, fails to maintain its beta-sheet structure and becomes denaured when the temperature is higher than 75 °C. (See, e.g., Ye et al., *Temperature and PH effects on biophysical and morphological properties of self-assembling peptide RADA16-I*, Journal of Peptide Science, 2008, 14(2), 152-62).

The Examiner also errs in alleging that "Farinas provides a number of polymeric matrices, including those claimed by Applicant (which is hydrophilic)" (See the Final Office Action, at page 4, last paragraph). As a matter of fact, Farinas does not disclose or suggest a drug reservoir of a hydrophilic polymer, only that of hydrophobic polymers or alternatively a

combination of hydrophobic and hydrophilic polymers. As a skiled artisan would appreciate, a drug reservoir of a combination of hydrophobic and hydrophilic polymers is not a matrix of a hydrophilic polymer as presently claimed. Furthermore, Farinas does not disclose nor suggest the use of peptides, polypeptides or proteins as active agents. Thus, the presently claimed method further distinguishes from that of Farinas in that claim 34 now recites and claims that the drug reservoir is a matrix of a hydrophilic polymer and that the active agent is a peptide, polypeptide or protein, which would not be considered by a person of ordinary skill in the art at the time the invention was made, as being useful patches that are applied to intact skin in which micro-channelshave been generated. Moreover, claim 34 as amended now recites and claims that achieving the therapeutic concentration of the peptide, polypeptide or protein is based on the delivery of said peptide, polypeptide or protein by diffusion only from the patch through the micro-channels in the subject's skin and into the blood. Thus, the presently claimed method is distinguishable from methods using other forms of administration, or patches of other agents.

In view of the above, none of cited references teaches or suggests that a peptide, polypeptide or protein can be delivered through a region of the skin where micro-channels have been generated from a patch comprising a drug reservoir layer being a matrix of a hydrophilic polymer and a pharmaceutical composition comprising said peptide, polypeptide or protein so as to achieve a therapeutic blood concentration of said peptide, polypeptide or protein for extended period of time. Moreover, there is no teaching or suggestion in the cited references or elsewhere in the art to motivate one of ordinary skill in the art to combine the teachings of Avrahami with the teachings of the other cited references to arrive at the presently claime dinvention.

Based on the foregoing, Applicant submits that the explanations provided herein overcome the Examiner's position that the claimed invention is obvious in view of the cited references. It is therefore respectfully requested that the rejections of the claims be withdrawn.

Respectfully submitted,

Date: October 24, 2011

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